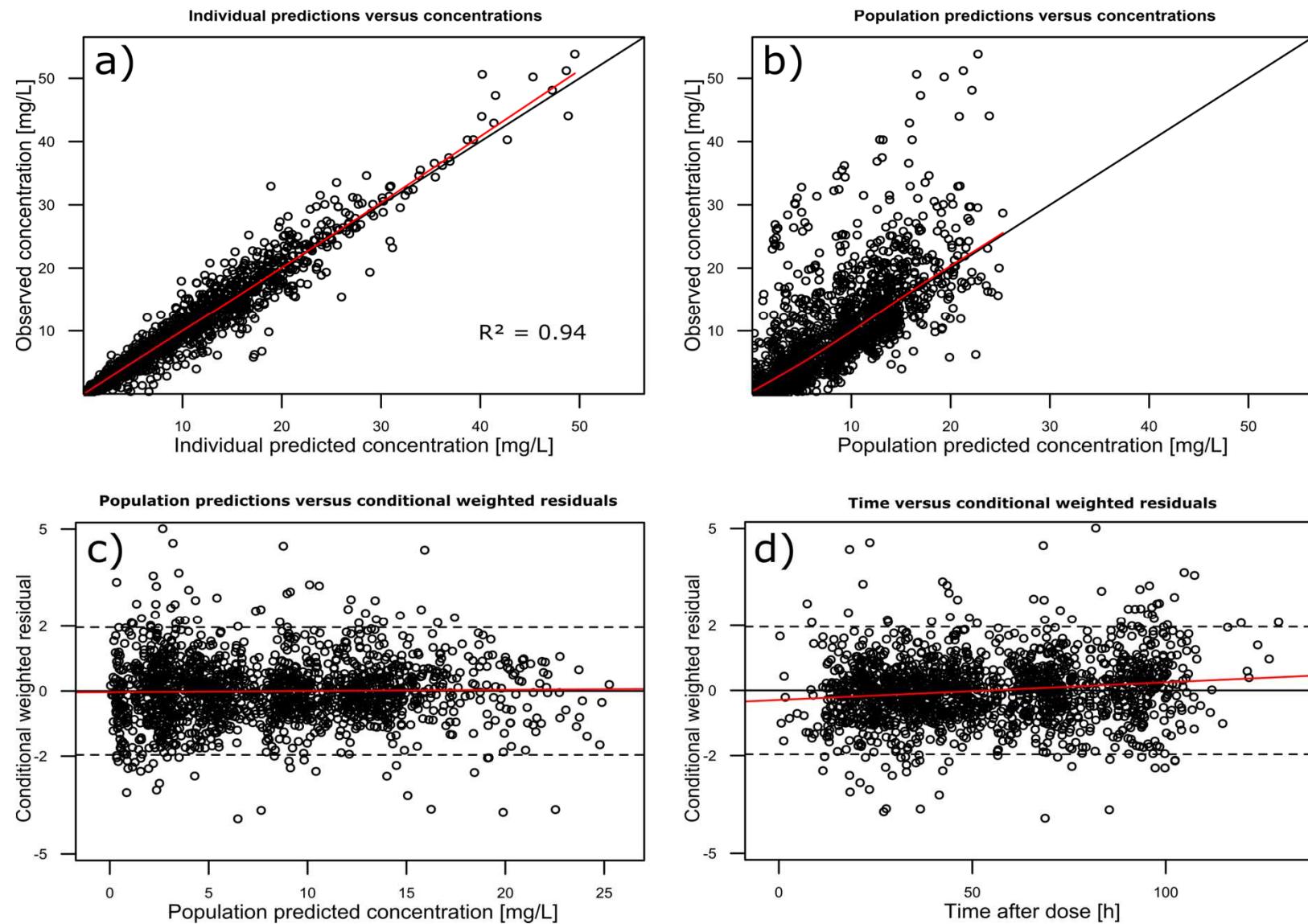


Study begin		↓					
Day			1	2	3	4	
Linezolid infusions		a	█	█	█	█	█
Time frame for sampling <sup>b</sup>							

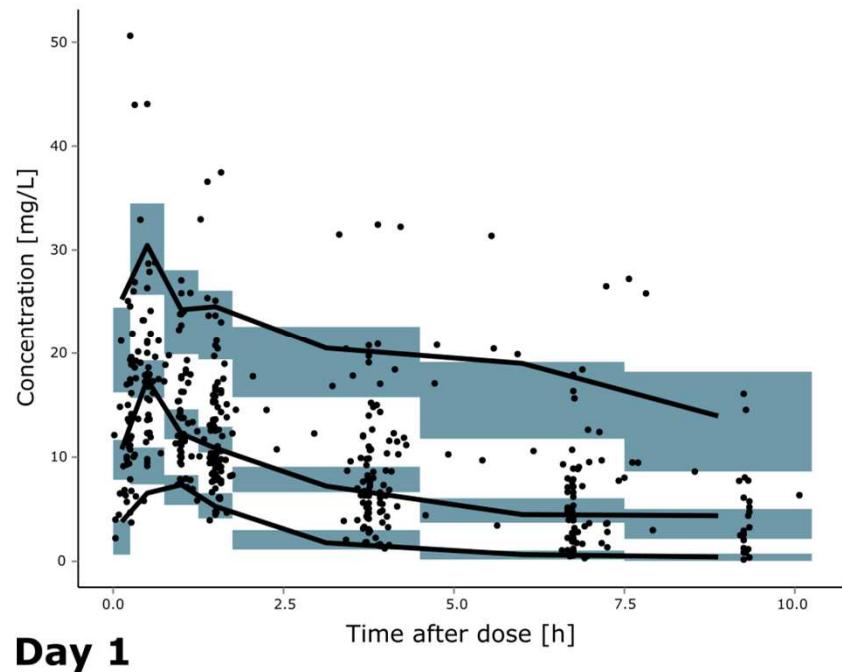
## **Supplemental Figure 1 Study protocol of blood sampling for linezolid determinations.**

<sup>a</sup>, zero to 4 linezolid infusions before study begin

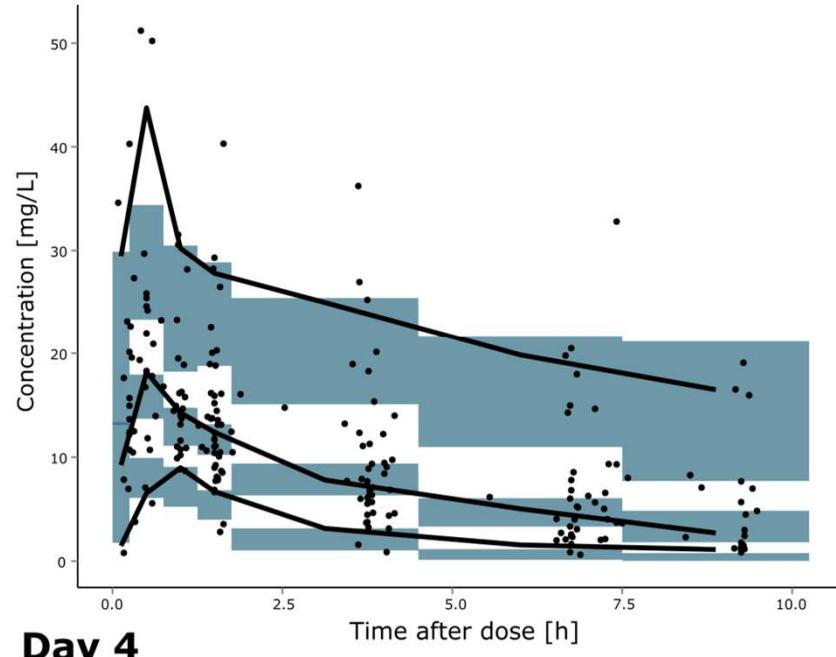
<sup>b</sup>, median 32 samples per patient over 4 days for determination of linezolid concentrations



**Supplemental Figure 2** Goodness of fit plots of covariate population pharmacokinetic model. Observed concentrations of linezolid are plotted against the individual post-hoc (a) and population predicted (b) concentration estimates. Conditional weighted residuals are plotted against population predicted concentrations (c) and time after dose (d).



**Day 1**



**Day 4**

**Supplemental Figure 3** Visual predictive checks of covariate population pharmacokinetic model on days 1 and 4. Measured concentrations (dots) are plotted with 5<sup>th</sup>, 50<sup>th</sup> and 95<sup>th</sup> percentile of measured data (black lines) and respective 95% prediction intervals from 1,000 simulations.

**Supplemental Table 1** Explorative data analysis for covariate candidates influencing linezolid pharmacokinetics in patient group 1<sup>1</sup> as determined by univariate analyses

Covariate	Correlation with trough values		Correlation with 1-hour postdose values	
	p < 0.01 on day	Lowest p-value (day)	p < 0.01 on day	Lowest p-value (day)
<b>Patient demographics</b>				
Sex	–	0.622 (4)	–	0.070 (1)
Age	–	0.030 (2)	–	0.220 (1)
Height	–	0.343 (2)	1,2	0.005 (1,2)
Weight	–	0.604 (4)	2	0.009 (2)
<b>Liver</b>				
ICG elimination rate <sup>2</sup>	–	0.047 (3)	–	0.122 (3)
Antithrombin	1,2,3,4	<0.001 (1,2)	1,2,3,4	<0.001 (1,2)
Bilirubin	1,2,3,4	0.003 (2)	–	0.028 (4)
Factor V	1,2,3	<0.001 (2)	2,3	<0.001 (2)
Fibrinogen	1,2,3	<0.001 (1,2)	1,2,3	0.002 (1)
INR	1,2	0.002 (2)	–	0.014 (2)
<b>Kidney</b>				
Creatinine clearance <sup>3</sup>	3,4	0.001 (4)	4	0.001 (4)
Creatinine in serum <sup>3</sup>	4	<0.001 (4)	–	0.013 (4)
Urine volume	1,2	0.001 (1)	–	0.019 (1)
<b>Acid-base balance</b>				
Bicarbonat	2,3	0.004 (3)	–	0.118 (3)
Lactate	1,3	<0.001 (1,3)	3,4	<0.001 (3)
<b>Disease</b>				
ARDS	2,3,4	<0.001 (3,4)	–	0.018 (3)
Peritonitis	1,2,3,4	0.001 (1)	–	0.041 (3)
Pneumonia	1,3	0.007 (1)	–	0.145 (2)
<b>Inflammation</b>				
C-reactive protein	3,4	0.002 (4)	–	0.087 (2)
Interleukin-6	–	0.272 (1,4)	–	0.773 (2)
<b>Severity of Disease</b>				
SOFA	–	0.027 (1)	–	0.369 (1)
APACHE II	–	0.379 (1)	–	0.382 (3)
<b>Specific treatments</b>				
CRRT	1,2	0.003 (2)	–	0.021 (2)
ECLA	2	0.005 (2)	–	0.058 (1)
Liver transplantation	–	0.021 (2)	–	0.219 (3)
Lung transplantation	–	0.291 (1)	–	0.725 (4)
<b>Genetics of P-glycoprotein</b>				
rs1128503	–	0.714 (1)	–	0.347 (2)
rs1045642	–	0.246 (4)	–	0.703 (3)
rs2032582	–	0.238 (3)	–	0.246 (2)
<b>Protein</b>				
Albumin	–	0.188 (4)	–	0.203 (4)

<sup>1</sup>, 52 study patients receiving linezolid (characteristics see Table 1); <sup>2</sup>, Indocyanine green elimination rate, determination of correlation coefficient only with linezolid concentrations on study day 3, because indocyanine green elimination rate was mostly determined at this day. <sup>3</sup>, Only non-CRRT-patients included in this calculation

Abbreviations: ALT, alanine aminotransferase; INR, International Normalized Ratio; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, Continuous Renal Replacement Therapy; ECLA, Extra-corporeal Lung Assist

The second trough value of each day was used.

**Supplemental Table 2** Effects on linezolid levels in patient group 1<sup>1</sup> as determined in multivariate analyses

Effects on trough values		
Covariate	p ≤ 0.0016 on day	Lowest p-value (day)
<b>Liver</b>		
Antithrombin	1,2,3	< 0.001 (2)
Bilirubin	n.s.	—
Factor V	n.s.	—
Fibrinogen	1,2	0.001 (1,2)
INR	n.s.	—
<b>Kidney</b>		
Creatinine clearance <sup>1</sup>	n.s.	—
Creatinine in serum <sup>1</sup>	n.s.	—
Urine volume	n.s.	—
<b>Acid-base balance</b>		
Bicarbonate	n.s.	—
Lactate	1,3	<0.001 (3)
<b>Disease</b>		
ARDS	3,4	<0.001 (3,4)
Peritonitis	n.s.	—
Pneumonia	n.s.	—
<b>Inflammation</b>		
C-reactive protein	3	<0.001 (3)
<b>Specific treatments</b>		
CRRT	n.s.	—
ECLA	n.s.	—
Effects on 1-hour postdose values		
<b>Patient size</b>		
Height	1	0.001 (1)
Weight	2	0.001 (2)
<b>Liver</b>		
Antithrombin	2	<0.001 (2)
Factor V	n.s.	—
Fibrinogen	1	<0.001 (1)
<b>Kidney</b>		
Creatinine clearance <sup>1</sup>	4	<0.001 (4)
<b>Acid-base balance</b>		
Lactate	3,4	<0.001 (3)

<sup>1</sup>, 52 study patients receiving linezolid (characteristics see Table 1); <sup>2</sup>, Only non-CRRT-patients included in this calculation; n.s., not significant (p > 0.0016)

Parameter	Median estimate	95% CI	Shrinkage [%]
CL	7.92 L/h	6.27 – 9.74 L/h	-
Q	65.59 L/h	45.92 – 109.61 L/h	-
Vc	15 L	8.58 – 20.67 L	-
Vp	26.55 L	21.24 – 32.63 L	-
KA	1.72 h <sup>-1</sup>	0.66 – 2.38 h <sup>-1</sup>	-
Weight on Vc <sup>1</sup>	1.31	0.70 – 2.35	-
Lactate on CL <sup>1</sup>	-0.21	-0.30 – -0.11	-
Fibrinogen on CL <sup>1</sup>	0.04	0 – 0.08	-
ARDS on CL <sup>1</sup>	1.82	1.26 – 2.62	-
Peritonitis on Vc <sup>1</sup>	1.53	1.16 – 2.11	-
$\omega_{CL}^2$ (%)	58	46 – 73	-0.74
$\omega_{Vc}^2$ (%)	37	23 – 61	13.77
$\sigma_{additive}^2$	0.005	0.001 – 0.008	-
$\sigma_{proportional}^2$	0.115	0.073 – 0.182	-

**Supplemental Table 3** Median estimates and 95% confidence intervals from bootstrap statistics (n=1000) of pharmacokinetic parameters (Vc = central volume of distribution, Vp = peripheral volume of distribution, CL = elimination clearance, Q = intercompartmental clearance, KA = absorption rate constant), coefficients of variation of inter-individual variability ( $\omega^2$ ) and variance estimates of residual unexplained variability ( $\sigma^2$ ). <sup>1</sup>Estimated covariate exponents/factors as used in equations for CL and Vc.